L4 ANSWER 1 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AB The invention relates to pharmaceutical compositions suitable for treating or curing clinical complications mediated by endotoxin, including sepsis. The compositions contain components suitable for detoxifying endotoxin rendering it less deleterious to mammals such as humans, in particular to patients with reduced host-defence resistance. The invention also relates to pharmaceutical compositions suitable for stimulating bone formation, e.g. for mending broken bone or for prophylaxis or therapy of metabolic bone diseases such as osteoporosis and osteomalacia and pharmaceutical compositions for decreasing or inhibiting undesired bone formation. The pharmaceutical compositions according to the invention are directed at modulating phosphatase activity in vivo.
AN 2001:549697 BIOSIS
DN PREV200100549697
TI Method of dephosphorylating an endotoxin in vivo with **alkaline phosphatase**.
AU **Poelstra, Klaas (1)**; Hardonk, Machiel Josephus; Bakker, Winston Willem; Meijer, Dirk KLaas Fokke
CS (1) Buitenpost Netherlands
ASSIGNEE: Rijksuniversiteit Groningen, Groningen, Netherlands
PI US 6290952 September 18, 2001
SO Official Gazette of the United States Patent and Trademark Office Patents, (Sep. 18, 2001) Vol. 1250, No. 3, pp. No Pagination. e-file.
ISSN: 0098-1133.
DT Patent
LA English

L4 ANSWER 2 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2002:320230 BIOSIS
DN PREV200200320230
TI Glomerular ecto-**Alkaline Phosphatase**: A renal protective molecule.
AU Kapojos, Jola J. (1); **Poelstra, Klaas**; Borghuis, Theo (1); Bakker, Winston W. (1)
CS (1) Department of Pathology and Laboratory Medicine, University Hospital, Groningen Netherlands
SO Journal of the American Society of Nephrology, (September, 2001) Vol. 12, No. Program and Abstract Issue, pp. 501A-502A. http://www.jasn.org/. print.
Meeting Info.: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology San Francisco, CA, USA October 10-17, 2001
ISSN: 1046-6673.
DT Conference
LA English

L4 ANSWER 3 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:534456 BIOSIS
DN PREV200100534456
TI A single injection of **alkaline phosphatase** significantly attenuates the inflammatory response upon lipopolysaccharide (LPS) in serum and in livers of mice.
AU **Poelstra, Klaas (1)**; Verweij, Willem R. (1); Bentala, Hafida (1); Huizinga-Van der Vlag, Ali (1); Meijer, Dirk K. (1)
CS (1) Univ of Groningen, Groningen Netherlands
SO Hepatology, (October, 2001) Vol. 34, No. 4 Pt. 2, pp. 279A. print.
Meeting Info.: 52nd Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA November 09-13, 2001
ISSN: 0270-9139.
DT Conference
LA English
SL English

L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2002 ACS

AB The authors disclose a method of diagnosis of onset of endotoxemia or sepsis due to Gram neg. bacterial infection comprising monitoring of the degree of AP occupancy of lipopolysaccharide (LPS) binding sites on **alk. phosphatase** in a sample of tissue or fluid derived from a patient, wherein the degree of AP occupancy is assocd. with presence or absence of Gram neg. bacterial infection. The authors disclose a kit comprising **alk. phosphatase** LPS binding site binding ligand and instructions for carrying out an assay according to any of the preceding claims and optionally any addnl. components required for such assay e.g. detectable marker, buffer, containers and comparative samples or data charts e.g. std. curves or data concerning relevant data of **alk. phosphatase** values. The authors describe a method for therapy of endotoxemia or sepsis said method comprising administration of a pharmaceutically effective amt. of the LPS binding site of **alk. phosphatase** in a systematically acceptable form with the proviso the ligand is neither **alk. phosphatase** nor a deriv. of **alk. phosphatase** having dephosphorylating activity. The authors propose a method for removing LPS from tissue or fluid said method comprising contacting the LPS binding site of **alk. phosphatase** with the tissue or fluid to be treated followed by sepn. of the LPS binding site and the tissue or fluid after the LPS binding site has bound the LPS present in the fluid or tissue, with the proviso the ligand is neither **alk. phosphatase** nor a deriv. of **alk. phosphatase** having dephosphorylating activity. A method of purifn. of AP itself from tissue or body fluids or other biol. prodn. systems with a compd. with an LPS binding site of **alk. phosphatase** such as LPS, lipid A or other ligand as described in the preceding claims is disclosed.

AN 2000:442019 CAPLUS

DN 133:55309

TI Diagnosis and therapy of sepsis using the LPS-binding moiety of **alkaline phosphatase** and a method of purification of **alkaline phosphatase** using LPS

IN **Poelstra, Klaas**; Meijer, Dirk Klaas Fokke; Man In 't Veld, Arie Jacob

PA Stichting Voor De Technische Wetenschappen, Neth.; Rijksuniversiteit Groningen

SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000037943	A1	20000629	WO 1998-NL722	19981221
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9917869	A1	20000712	AU 1999-17869	19981221
EP 1141717	A1	20011010	EP 1998-962694	19981221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI WO 1998-NL722 A 19981221

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2002 ACS

AB The present invention relates to a compd. comprising a carrier mol., said carrier mol. being linked to a further mol., said further mol. being at least one cyclic peptide, said cyclic peptide comprising in the cyclic peptide portion thereof at least one sequence encoding a cell receptor recognizing peptide (RRP) and with the proviso that the compd. is not a naturally occurring receptor agonist or antagonist. Preferably, the RRP is of a receptor specific for Hepatic Stellate Cells (HSC) or a receptor that is upregulated on HSC during disease. In particular, the RRP may be of a receptor selected from the group of PDGF receptor, collagen type VI receptor, cytokine receptor(s) such as TGF.beta., IFN.alpha. and interleukin 1.beta.. Preferably, the cyclic portion of the cyclic peptide comprises at least the amino acid sequence RGD or KPT. The compds. can be used as an active targeting ingredient for manufg. a pharmaceutical compn. for therapy, prophylaxis or diagnosis of a disease selected from the group consisting of fibrotic disease, sclerotic disease and chronic or acute inflammatory processes such as glomerulosclerosis, interstitial fibrosis, lung fibrosis, atherosclerosis, rheumatoid arthritis, Crohn's disease, colitis ulcerosa, glomerulonephritis and sepsis, in particular for targeting HSC. The invention also relates to pharmaceutical compns. comprising the above compd.(s).

AN 2000:277884 CAPLUS

DN 132:313679

TI Peptide-based carrier devices for hepatic stellate cells

IN **Poelstra, Klaas**; Beljaars, Eleonora; Meijer, Dirk Klaas Fokke; Schuppan, Detlef Bruno Igor

PA Stichting voor de Technische Wetenschappen, Neth.; Rijksuniversiteit te Groningen

SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000023113	A1	20000427	WO 1998-NL579	19981008
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9895609	A1	20000508	AU 1998-95609	19981008
	EP 1117443	A1	20010725	EP 1998-949252	19981008
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	WO 1998-NL579	A	19981008		

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 2000:490147 BIOSIS

DN PREV200000490268

TI **Alkaline phosphatase** attenuates the response of macrophages upon lipopolysaccharide (LPS); a potential role for this enzyme during cholestasis.

AU **Poelstra, Klaas (1)**; Bentala, Hafida (1); Verweij, Willem R. (1); Meijer, Dirk K. F. (1)

CS (1) Groningen Univ Institute for Drug Exploration (GUIDE), Groningen Netherlands

SO Hepatology, (October, 2000) Vol. 32, No. 4 Pt. 2, pp. 198A. print.
Meeting Info.: 51st Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA

October 27-31, 2000 American Association for the Study of Liver Diseases . ISSN: 0270-9139.
DT Conference
LA English
SL English

L4 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AB Natural substrates for **alkaline phosphatase** (AP) are at present not identified despite extensive investigations. Difficulties in imagining a possible physiological function involve its extremely high pH optimum for the usual exogenous substrates and its localization as an ecto-enzyme. As endotoxin is a substance that contains phosphate groups and is usually present in the extracellular space, we studied whether AP is able to dephosphorylate this bacterial product at physiological pH levels. We tested this in intestinal cryostat sections using histochemical methods with endotoxin from Escherichia coli and Salmonella minnesota R595 as substrate. Results show that dephosphorylation of both preparations occurs at pH 7.5 by AP activity. As phosphate residues in the lipid A moiety determine the toxicity of the molecule, we examined the effect of the AP inhibitor levamisole in vivo using a septicemia model in the rat. The results show that inhibition of endogenous AP by levamisole significantly reduces survival of rats intraperitoneally injected with E. coli bacteria, whereas this drug does not influence survival of rats receiving a sublethal dose of the gram-positive bacteria Staphylococcus aureus. in view of the endotoxin-dephosphorylating properties of AP demonstrated in vitro, we propose a crucial role for this enzyme in host defense. The effects of levamisole during gram-negative bacterial infections and the localization of AP as an ecto-enzyme in most organs as well as the induction of enzyme activity during inflammatory reactions and cholestasis is in accordance with such a protective role.
AN 1997:499715 BIOSIS
DN PREV199799798918
TI Dephosphorylation of endotoxin by **alkaline phosphatase** in vivo.
AU **Poelstra, Klaas (1)**; Bakker, Winston W.; Kolk, Pieter A.; Kamps, Jan A. A. M.; Hardonk, Machiel J.; Meijer, Dirk K. F.
CS (1) Dep. Pharmacokinetics Drug Delivery, Univ. Groningen, Ant. Deusinglaan 1, 9713 Av Groningen Netherlands
SO American Journal of Pathology, (1997) Vol. 151, No. 4, pp. 1163-1169. ISSN: 0002-9440.
DT Article
LA English

L4 ANSWER 8 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
AB **Alkaline phosphatase** (AP), a common enzyme present in many species including humans, has been studied extensively. Although the enzyme is routinely applied as a marker for liver function, its biologic relevance is poorly understood. The reason for this is obvious: the pH optimum of AP in vitro, as measured with the usual test substrates (+- 10.5), greatly exceeds the physiologic pH range as it occurs in biologic tissues. We now hypothesize that this relatively high pH optimum in vitro is related to dissociation of acidic groups in the protein preparation, which leads to the formation of negatively charged groups in the vicinity of the active site of the enzyme. These negatively charged groups may promote the activity of AP. We examined the possibility that endotoxin is a natural substrate for this enzyme because this phosphorylated substance is able to supply multiple negatively charged residues in the microenvironment of the enzyme at a physiologic pH level. Phosphate groups in the endotoxin molecule are known to be essential for the biologic activities of this bacterial product. The present study demonstrates that in intestinal and renal tissue specimens in vitro, AP is endowed with endotoxin dephosphorylating activity at pH levels closer to the physiologic range. This is also illustrated by our experiments in vivo showing that the toxicity of endotoxin is significantly reduced after

exposure to AP preparations, as tested by inducing a local intradermal inflammatory reaction in rats. Collectively, our data suggest that the ubiquitous enzyme AP may accomplish protection against endotoxin, an equally ubiquitous product of Gram-negative bacteria that may cause lethal complications after an infection with these micro organisms.

AN 1997:225133 BIOSIS
DN PREV199799516849
TI A physiologic function for **alkaline phosphatase**: Endotoxin detoxification.
AU **Poelstra, Klaas (1)**; Bakker, Winston W.; Klok, Pieter A.; Hardonk, Machiel J.; Meijer, Dirk K. F.
CS (1) Dep. Pharmacokinetics Drug Delivery, Univ. Groningen, A. Deusinglaan 1, 9713 AV Groningen Netherlands
SO Laboratory Investigation, (1997) Vol. 76, No. 3, pp. 319-327. ISSN: 0023-6837.
DT Article
LA English

RBI.L2

L4 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2002 ACS
AB Pharmaceutical compns. are disclosed for treating or curing clin. complications mediated by endotoxin, including sepsis. The compns. contain components suitable for detoxifying endotoxin rendering it less deleterious to mammals such as humans, in particular to patients with reduced host-defense resistance. Also disclosed are pharmaceutical compns. for stimulating bone formation, e.g. for mending broken bone or for prophylaxis or therapy of osteoporosis, as well as pharmaceutical compns. for decreasing or inhibiting undesired bone formation. The pharmaceutical compns. of the invention are directed at modulating phosphatase activity in vivo. **Alk. phosphatase** was shown to attenuate endotoxin toxicity in vitro at physiol. pH. Other data demonstrated that endotoxin treated with **alk. phosphatase** exhibits reduced toxicity in vivo, and that al. phosphatase may be able to detoxify endotoxin in vivo.
AN 1995:551086 CAPLUS
DN 122:282263
TI Pharmaceutical composition comprising phosphatase or a derivative thereof for treating endotoxin-mediated pathology and pathology involving bone formation
IN **Poelstra, Klaas**; Hardonk, Machiel Josephus; Bakker, Winston Willem; Meijer, Dirk Klaas Fokke
PA Rijksuniversiteit te Groningen, Neth.
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9505455	A1	19950223	WO 1993-NL171	19930813
	W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9348356	A1	19950314	AU 1993-48356	19930813
	WO 9505456	A1	19950223	WO 1994-NL189	19940810
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
	RW: KE, MW, SD, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9477101	A1	19950314	AU 1994-77101	19940810
	AU 698331	B2	19981029		
	EP 721501	A1	19960717	EP 1994-927860	19940810

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE

	JP 09502342	T2	19970311	JP 1994-506872	19940810
	US 6290952	B1	20010918	US 1996-596297	19960410
	AU 9914243	A1	19990401	AU 1999-14243	19990128
PRAI	WO 1993-NL171	W	19930813		
	AU 1994-77101	A3	19940810		
	WO 1994-NL189	W	19940810		

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FULL ESTIMATED COST	32.17	32.38

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.86	-1.86

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